

Public Health. Author manuscript; available in PMC 2007 September 24.

Published in final edited form as:

Public Health. 2007 September; 121(9): 643-655.

Effects of aerobic exercise on lipids and lipoproteins in adults with type 2 diabetes:

a meta-analysis of randomized-controlled trials

G.A. Kelley* and K.S. Kelley

School of Medicine, Department of Community Medicine, West Virginia University, PO Box 9190, Morgantown, West Virginia

Summary

Objective—To conduct a meta-analysis of randomized-controlled trials in order to examine the effects of 8 weeks or more of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes.

Methods—Studies were included if total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), ratio of TC to HDL-C (TC/HDL-C), triglycerides (TG), or all of the above, were assessed. A secondary outcome was glycosylated haemoglobin (HbA₁).

Results—Seven studies representing 220 men and women (112 exercise, 108 control) were available for pooling. Using a random-effects model, a statistically significant reduction of about 5% was found for LDL-C, whereas no statistically significant improvements were found for TC, HDL-C, TC/HDL-C or TG. A trend for a statistically significant reduction in HbA₁ was also found.

Conclusions—Although our overall results suggest that aerobic exercise lowers LDL-C in adults with Type 2 diabetes, additional randomized-controlled trials are needed on this topic.

Keywords

Exercise; Lipids; Cholesterol; Meta-analysis; Diabetes

Introduction

Cardiovascular disease (CVD), the number one cause of mortality in the USA, ¹ is almost twice as common in individuals with diabetes. ² A significant risk factor for cardiovascular disease is less than optimal lipid and lipoprotein levels. ³ Aerobic exercise, a low-cost therapeutic lifestyle change that is available to most of the general public, has been recommended for improving lipid and lipoprotein levels in adults, including those with diabetes. ³ Unfortunately, previous randomized-controlled trials investigating the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes, the most common form of diabetes, have led to less than overwhelming results. ⁴⁻¹⁰ For example, none of the results for total cholesterol from the aforementioned randomized-controlled trials were reported by the authors as statistically significant, whereas 29% of high-density lipoprotein cholesterol (HDL-C) outcomes, 14% of low-density lipoprotein cholesterol (LDL-C) outcomes, 29% of total

^{*}Corresponding author. Tel.: +304 293 6279; fax: +304 293 5891. E-mail address: gkelley@hsc.wvu.edu (G.A. Kelly)

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

cholesterol (TC)/HDL-C outcomes, and 29% of triglyceride (TG) outcomes were reported as statistically significant. One of the possible reasons for the lack of statistically significant findings may have to do with the small sample sizes included in these studies. Meta-analysis is a quantitative approach for pooling the results of studies in an attempt to arrive at an overall conclusion regarding a body of evidence. It is especially useful when the number of studies is small, the number of subjects that can be enrolled in the studies is small, or both. 11 This is the case with the randomized-controlled trials that have examined the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes. In addition, we, as well as others ¹² are not aware of any meta-analytic research that has focused solely on the effects of aerobic exercise on lipids and lipoproteins when limited to adults with Type 2 diabetes. Thus, given (1) the increased risk for CVD in adults with Type 2 diabetes, (2) the increased risk for CVD in individuals with less than optimal lipid and lipoprotein levels, (3) the less than overwhelming results of randomized controlled trials dealing with the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes, and (4) the absence of any meta-analytic work that has specifically focused on the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes, the primary purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes.

Materials and methods

Data sources

Studies for this meta-analysis were obtained from (1) computerized literature searches (MEDLINE, EMBASE, SportDiscus, Current Contents, Dissertation Abstracts International); (2) cross-referencing from review articles as well as original trials; (3) hand searching selected journals; and (4) expert review of our reference list (Dr. William Haskell, personal communication). Key words used in our computerized literature searches included exercise, cholesterol, diabetes, physical activity, fitness, lipids, lipoproteins, adults, humans, and cardiovascular disease.

Study selection

The selection of studies was conducted by both authors, independent of each other. Disagreements were resolved by consensus. The inclusion criteria for this study were as follows: (1) randomized-controlled trials with a comparative non-exercise group; (2) prescribed aerobic exercise (no diet intervention) of at least 3 days per week for 8 weeks or longer; (3) adults aged 18 years or older; (4) all individuals classified by study authors as having Type 2 diabetes; (5) studies published in journal, dissertation, or master's thesis format; (6) studies published in the English-language; (7) studies published between January 1 1955 and October 1 2006; and (8) assessment of one or more of the following lipid, lipoproteins in the fasting state, or both: TC, HDL-C, LDL-C, TC/HDL-C and TG. Multiple publication bias was addressed by examining each potentially eligible study and only including data from the one study that provided the greatest amount of information. We did not include foreign-language articles because they were beyond the scope of this investigation. In addition, studies that were limited to progressive resistance training (weight training), ¹³ or a combination of progressive resistance training and aerobic exercise ^{14,15} were excluded.

Data abstraction

A coding form that could hold more than 200 items per study was used for this investigation. The major categories of variables that were coded included (1) study characteristics (e.g. source, study quality, percent dropout); (2) subject characteristics (e.g. gender, age, body weight, diabetes duration, race and ethnicity, tobacco use, dietary therapy, hormone replacement therapy in women); (3) lipid assessment characteristics (e.g. time of day, number

of hours fasted), (4) training programme characteristics (e.g. length, frequency, intensity, duration, mode); (5) primary outcomes (TC, HDL-C, LDL-C, TC/HDL-C, TG); and (6) secondary outcomes (glycosylated haemoglobin (HbA₁), glucose, insulin, body weight, percent fat, body mass index and fitness, defined as changes in maximum oxygen consumption). Secondary outcomes were only included for those studies in which lipid and lipoprotein data were available. All studies were coded by both authors, independent of each other. Both authors then reviewed every data point for accuracy and consistency. Discrepancies were resolved by consensus. If consensus could not be reached, the consultant acted as an arbitrator until consensus was reached. Cohen's kappa for inter-rater agreement between the two coders before correcting discrepant items was 0.92.

Statistical analysis

Power estimates—Before conducting our statistical analysis, we performed power calculations designed specifically for meta-analytic data sets (traditional power analysis procedures are not appropriate for meta-analysis) for our primary and secondary outcomes based on the number of studies and outcomes that met our inclusion criteria. ¹⁶ Using a standardized effect size of 0.50, a random-effects variance component of 0.33, and the number of outcomes and average number of subjects available for each variable, the power to detect a statistically significant difference at a two-tailed alpha level of 0.05 and a power of 80% was 0.89 for TC and HDL-C, 0.88 for TG, 0.77 for LDL-C and TC/HDL-C, and 0.81 for HbA₁. We were not adequately powered to statistically examine for changes in glucose (0.69), insulin (0.38), body weight (0.58), percent body fat (0.11), body mass index (0.27) or changes in maximum oxygen consumption (0.26).

Primary and secondary outcomes—The primary outcomes in this study were baseline to final changes in TC, HDL-C, LDL-C, TC/HDL-C and TG reported in both milligrams per deciliter (mg/dl) and millimoles (mmol). Net changes in lipids and lipoproteins were calculated as the difference (exercise minus control) of the changes (final minus initial) in the mean values from each study. Pooled treatment effects were calculated by assigning weights equal to the inverse of the variance for net changes in all lipid and lipoprotein outcomes. A random-effects model was used for all analyses. ^{17,18} If the 95% confidence intervals did not cross zero (0), the results were considered to be statistically significant. Statistical heterogeneity was examined using the Q statistic. ¹⁹ The alpha value for the statistical significance of Q was set at $P \le 0.10$ because this statistic tends to suffer from low power. ²⁰ Because of this low power, we also examined the consistency of our overall results using a recently developed statistic (I^2) that is an extension of Q. ²¹ I^2 is calculated as $100\% \times (Q-df)/Q$, where Q is the heterogeneity statistic and df, the degrees of freedom. Values of 25%, 50%, and 75% are considered to be indicative of low, moderate and high degrees of heterogeneity. Our secondary outcome (changes in HbA₁) was analyzed using the same general procedures as for primary outcomes.

Publication bias was assessed using regression analysis to detect funnel plot asymmetry 22 and was considered to be statistically significant at a two-tailed alpha level of $P \le 0.05$. Study quality was assessed by the authors using a previously validated and reliable quality index developed by Jadad et al. 23 This assessment is a three-item questionnaire designed to assess bias, specifically, randomization, blinding, and withdrawals and dropouts. The minimum number of points possible is 0 and the maximum 5, with the higher number representing greater study quality. However, as there is currently no 'gold standard' for assessing the quality of a clinical trial, all such approaches need to be interpreted with caution. 24

In order to examine the effects of each study on the overall results for each primary outcome, analyses were conducted with each study deleted from the model once.

Meta-regression—In order to examine the relationship between lipid and lipoprotein outcomes and selected variables, simple, weighted, generalized least-squares random effects meta-regression was performed a priori and separately for each lipid and lipoprotein outcome. Meta-regression is analogous to simple and multiple regression for conventional datasets. Variables that were examined included country (USA vs other), whether all participants in the studies were overweight, obese, or both, at the start of the study (yes vs no), whether the exercise participants in the studies reduced their body weight (yes vs no), initial lipid levels, study quality, age, length, frequency, intensity, and duration of training as well as total minutes of training (length × frequency × duration). We were unable to report quantitative data for body weight because of a lack of reported data for such. In addition, we were unable to conduct any type of multiple regression analysis because of missing data for different variables from different studies, a common occurrence with meta-analytic data sets. ²⁵ If the 95% confidence intervals for the correlation coefficients did not cross -zero (0) the results were considered to be statistically significant. With the exception of study quality, which is reported as the median, descriptive statistics are reported as mean \pm standard deviation (X \pm SD) whereas primary and secondary outcome data are reported as the mean along with their 95% confidence intervals (X, 95% CI).

Results

Study characteristics

Of the 3750 citations reviewed, 10 met our inclusion criteria. $^{4-10,26-28}$ However, we were unable to obtain lipid data from three studies. $^{26-28}$ Thus, a total of seven studies were included in our final analysis (Table 1). $^{4-10}$ The primary reason for exclusion of the other studies was that all participants in the studies did not have Type 2 diabetes. All of the included studies were parallel group trials and seemed to use an analysis-by-protocol approach in the analysis of their data. A total of 14 groups (seven exercise, seven control) representing 220 men and women (112 exercise, 108 control) and up to seven outcomes were available for pooling. The percentage of participants that were not available for follow-up assessment for those studies that reported such ranged from 5-20% for the exercise groups ($X \pm SD$, $14\% \pm 8\%$) and 5-23% for the control groups ($X \pm SD$, $12\% \pm 10\%$). Median study quality was 1. Three of the studies were conducted in the USA, 5,9,10 whereas one each was conducted in the Netherlands, 6 Israel, 7 Finland 8 and France. 4

Participant characteristics

Baseline characteristics of the participants are shown in Table 2. One study included only women, ¹⁰ another was limited to men, ⁴ whereas the remaining five included both men and women. ⁵⁻⁹ Two of the studies reported that all women were postmenopausal, ^{6,10} although the age ranges would suggest that most, if not all, women were postmenopausal. For the six studies that reported the gender distribution of participants that were available for follow-up, there were 74 women and 95 men. ^{4,5,7-10} None of the studies reported specific information on race. One study reported that none of the participants was taking any type of medication(s) that could affect lipids and lipoproteins, ¹⁰ whereas another study reported that participants were taking some type of medication that might affect lipids and lipoproteins. ⁶ In relation to diabetes treatment before the start of the study, one reported treatment with either diet alone, oral agents or insulin, ⁵ a second reported treatment with oral glucose-lowering drugs or insulin, ⁶, a third reported treatment with diet, glibenclamide and metformin, ⁷ a fourth reported treatment with diet alone, sulphonylurea, metformin, or both, ⁸ a fifth reported that none of the participants were taking any type of hormone replacement therapy or pharmacologic therapy for Type 2 diabetes (oral hypoglycemic agents or insulin), ¹⁰, a sixth reported that participants were taking oral hypoglycaemic medications but not insulin, ⁹ and a seventh reported that participants continued to take their diabetic medication, if any, during the study as well as

maintaining their usual diet.⁴ Five studies reported that the participants had Type 2 diabetes for at least 1 year, ⁵⁻⁸, ¹⁰ whereas another reported that participants had Type 2 diabetes for at least 3 months.⁹ For cigarette smoking, one study reported that none of the participants were cigarette smokers, ¹⁰ whereas two reported that some of the participants smoked.^{6,9} One study reported that some of the participants consumed alcoholic beverages. ¹⁰ Although all of the studies had participants maintain their usual diet throughout the intervention period, ⁴⁻¹⁰ one reported that one or more participants had introduced changes to their diet during the study that may have possibly influenced lipid and lipoprotein levels. ¹⁰ Four studies reported that none of the participants were physically active before taking part in the study, ^{4,5,9,10} whereas one reported that some participants were physically active before taking part in the study.⁷

Lipid assessment characteristics

All seven studies reported the assessment of lipids and lipoproteins in the morning after an overnight fast. $^{4-10}$ The number of hours fasted ranged from 10-12 h (X \pm SD, 11.5 \pm 0.8 h). One study reported that the participants refrained from exercise for at least 72 h before the assessment of lipids and lipoproteins. 6

Training program characteristics

Length of training ranged from 10-26 weeks ($X \pm SD$, 15.1 \pm 5.5 weeks), frequency from three to seven times per week ($X \pm SD$, 4.2 \pm 1.8 times per week), intensity from 65-73% of VO_{2max} ($X \pm SD$, 68.3 \pm 3.0%), duration from 30-75 min per session ($X \pm SD$, 47.1 \pm 14.4 min per session), and total minutes of training from 1050-4320 min ($X \pm SD$, 2,975 \pm 1,323 min). For training modality, one was limited to cycle ergometry, 4 two used walking, 5,10 two included walking, jogging, cycling, and swimming, 6,7 and one used walking, jogging and skiing. Another study, which assessed physical activity with a pedometer, probably consisted primarily, if not solely, of walking. Compliance to the exercise protocol, defined as the percentage of exercise sessions attended, was about 69% for the one study that reported this information.

Primary and secondary outcomes

As can be seen in Table 3 and Figures 1-5, changes in TC, HDL-C, LDL-C, TC/HDL-C, and TG were in the direction of benefit but only reductions in LDL-C were statistically significant. Changes in lipids and lipoproteins were equivalent to reductions of about 2%, 2%, 5%, 6%, and 5%, respectively, for TC, HDL-C, LDL-C, TC/HDL-C, and TG. Statistically significant heterogeneity was observed for HDL-C and the ratio of TC to HDL-C but not TC, LDL-C, or TG. No statistically significant publication bias was observed for TC (P = 0.99), HDL-C (P = 0.12), LDL-C (P = 0.89), TC/HDL-C (P = 0.21) or TG (P = 0.46).

With each study deleted from the model once, pooled changes in TC remained non-significant, ranging from -4.9 mg/dl (95% CI -10.5 to 0.6 mg/dl; -0.13 mmol, 95% CI -0.27 to 0.02 mmol) to -2.5 mg/dl (95% CI -8.4 to 3.3 mg/dl; -0.06 mmol, 95% CI, -0.22 to 0.09 mmol). For HDL-C, changes also remained non-significant, ranging from 1.7 mg/dl (95% CI -1.3 to 4.7 mg/dl; 0.04 mmol, 95% CI -0.03 to 0.12 mmol) to 0.2 mg/dl (95% CI -2.5 to 2.9 mg/dl; 95% CI 0.20, mmol, 95% CI -0.06 to 0.08 mmol). Changes in LDL-C ranged from a significant reduction of -8.8 mg/dl (95% CI -15.2 to -2.6 mg/dl; -0.23 mmol, 95% CI -0.39 to -0.07 mmol) to a non-significant reduction of -4.2 mg/dl (95% CI -10.6 to 2.2 mg/dl; -0.11 mmol, 95% CI -0.27 to 0.06 mmol). For the ratio of TC/HDL-C, changes ranged from a significant reduction of -0.5 (95% CI -0.94) to a non-significant reduction of -0.1 (95% CI -0.5 to 0.2). Triglycerides ranged from a non-significant reduction of -13.7 mg/dl (95% CI -35.4 to 8.0 mg/dl; -0.16 mmol, 95% CI -0.40 to 0.09 mmol) to -6.5 mg/dl (95% CI -20.9 to 7.9 mg/dl; -0.07 mmol, 95% CI -0.24 to 0.09 mmol). There was a trend for a statistically significant decrease in HbA1 (Table 3 and Figure 6).

Meta-regression

Greater reductions in TC were associated with studies conducted in the USA compared with other countries (r = 0.89, 95% CI 0.37 to 0.98). No other statistically significant associations were observed for changes in TC, HDL-C, LDL-C, TG, and TC/HDL-C and any of the other variables assessed, including baseline levels of lipids and lipoproteins.

Discussion

Interpretation of research findings

The purpose of this study was to use the meta-analytic approach to examine the effects of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes. Although changes in the direction of benefit were found for TC, HDL-C, LDL-C, TC/HDL-C and TG, only decreases in LDL-C were statistically significant when results were pooled. However, reductions in LDL-C remained statistically significant only when the study by Ligtenberg et al. was deleted from the model. Similar to the findings for LDL-C, changes in the ratio of TC to HDL-C were only statistically significant when the study by Ligtenberg et al.⁶ was deleted from the model. Unfortunately, we could not identify any definitive factor(s) that made the study by Ligtenberg et al. 6 different from the other included studies. However, it is possible that the results from the study by Ligtenberg et al. 6 could have been influenced by the fact that several participants were taking simvastatin before and during the intervention period. The former notwithstanding, this finding should be interpreted with caution as most of our other included studies did a poor job of reporting this information, and thus may have also had participants taking lipid-lowering drugs. Given the sensitivity of these findings, our overall results need to be interpreted with caution. The statistically significant association between greater changes in TC from studies published in the USA compared with other countries may have to do with country bias²⁹ (i.e. the possibility that the USA may be more biased towards publishing studies that yielded positive results in relation to the effects of exercise on lipids and lipoproteins in adults). Alternatively, this finding could be nothing more than the play of chance given the large number of statistical tests we ran, a consequence of the inability to control for other factors given the small number of studies included, or both. The lack of association observed between changes in lipids and lipoproteins and such factors as initial lipid levels may be the result of regression dilution bias (attenuation by errors). However, as corrections for regression dilution bias are controversial, no such adjustments were made. 30 Our lipid and lipoprotein findings differ somewhat compared with two less restrictive metaanalyses dealing with the effects of exercise in participants with Type 2 diabetes. 31,32 For example, Yoo and Lee³¹ found that regular exercise had a positive effect on TC, HDL-C, and LDL-C in people with Type 2 diabetes, whereas Thomas et al.³² reported statistically significant reductions in TG but not TC, HDL-C, or LDL-C. One of the possible reasons for the discrepant findings between both these meta-analyses as well as ours may have to do with the different inclusion criteria. For example, in our study, we limited the inclusion of studies to aerobic exercise with no apparent dietary intervention, whereas the other two meta-analyses included both aerobic and resistance training studies as well as studies in which exercise groups were placed on a diet. 31,32

Although not the primary outcome of our study, changes in HbA_1 approached statistical significance. These findings are similar to the statistically significant improvements observed in three previous meta-analyses that have examined the effects of exercise on HbA_1 . $^{31-33}$

Clinical implications

Although aerobic exercise should almost always be recommended because of the numerous other benefits that can be derived from it,³⁴ it seems that people with Type 2 diabetes may need to be treated aggressively with lipid-improving drugs and a rigorous diet.³ The former

notwithstanding, the approximate 5% reduction in LDL-C may be clinically important. For example, it has been shown that every 1% reduction in LDL-C reduces coronary risk by about 1.7%. Thus, our observed changes in LDL-C, currently the primary target of lipid-lowering treatment in adults, would be equivalent to an 8.5% reduction in coronary risk. In addition, a 1% decrease in HDL-C has been associated with up to a 3% increase in the risk for coronary heart disease. On the basis of our findings, this should translate into a reduction in coronary risk of about 6%.

It is important to realize that recent research has found that the benefits of aerobic exercise may not be derived so much from the improvement of lipids and lipoproteins measured in the clinical setting but rather from changes in the physical structure of protein particles that carry cholesterol through the bloodstream. Traus et al., Tin their 24-week study, examined 111 sedentary, overweight men and women who were randomly assigned to one of three intervention groups (walking 12 miles per week, jogging 12 miles per week, jogging 20 miles per week) or a control group. The authors found that all three exercise programmes increased the large, less dense protein particles that are less likely to contribute to atherosclerosis even if the subjects' TC did not change.

Our observed changes in HbA_1 are probably important in relation to the prevention of CVD in adults with Type 2 diabetes. For example, a recent meta-analysis that examined the association between HbA_1 and CVD in adults with diabetes found that chronic hyperglycemia is associated with an increased risk for CVD in adults with diabetes.³⁸

As most, if not all, of our studies in this meta-analysis adhered to the American College of Sports Medicine's guidelines for aerobic exercise, ³⁹ adherence to these guidelines should generally bring about the changes observed in our meta-analysis. This includes any activity that uses large muscle groups (e.g. brisk walking, jogging, cycling) carried out three to five times per week at an intensity of 40-85% of maximum oxygen uptake reserve for 20-60 continuous min. ³⁹ Lower intensity activities such as brisk walking compared with fast running may be preferable because of increased compliance and a lower risk for injury. ³⁹ In addition, as all of our studies included an exercise intervention of at least 8 weeks, it is highly unlikely that the length of training was responsible for the lack of detectable effects for TC, HDL-C and TG. ³⁹

Research implications

In addition to trying to reach some general conclusions about a body of research, it is also the meta-analyst's responsibility to provide suggestions for future research and to try and point out weaknesses in the included data that could effect the interpretation and generalizability of one's results. This latter factor is common to all meta-analyses. First, all of the studies seemed to use an analysis-by-protocol vs intention-to-treat approach in the analysis of their data. Consequently, it would seem plausible to suggest that future studies report both types of analyses in order to examine both the efficacy (does the treatment work?) and effectiveness (does the treatment work in the real world?) of aerobic exercise on lipids and lipoproteins in adults with Type 2 diabetes. Second, several participant characteristics were under-reported in our included studies. These included race and ethnicity, cigarette smoking, alcohol consumption, and the use of medications for hyperlipidaemia. The lack of reported information on medications for hyperlipidaemia is especially relevant, as some of the studies took place during the pre-statin era and the baseline values of lipids and lipoproteins in these participants would not be at current goals for people with diabetes³ An important research question that should be addressed in the future is the magnitude of benefit that aerobic exercise has on lipids and lipoproteins with the newer and more effective medications that are now available. A third suggestion is that future studies include quantitative data for body weight and changes in fitness (e.g. changes in maximum oxygen consumption). This is especially true given the effect that

these variables might have on changes in lipids and lipoproteins as a result of aerobic exercise in people with Type 2 diabetes. Furthermore, it is suggested that future studies report information on the number of hours that participants refrained from exercising before the assessment of lipids and lipoproteins as well as the compliance of participants to the exercise protocol. For example, the fact that only one study reported the number of hours that participants refrained from exercise before the assessment of lipids and lipoproteins could have influenced our findings. Although we believe that most, if not all, studies did have participants refrain from exercise for at least 24 h, this information was not reported, possibly because of the page limitations now imposed by most journals. This may also be a factor in the reporting of other data. Finally, the fact that some of our results were influenced by the deletion of studies from the model suggests that additional, randomized-controlled trials in this area are needed. This is especially true given the conflicting findings between our meta-analysis and two previous meta-analyses on this topic. 31,32

The fact that we conducted a large number of statistical analyses, particularly simple metaregression analyses, increases the possibility that some of our statistically significant findings may have been the result of chance. In addition, it is important to not try and generalize our findings beyond the range of subject and treatment characteristics included in our studies.

Conclusion

Our overall results suggest that aerobic exercise lowers LDL-C in adults with Type 2 diabetes. However, a need exists for additional randomized-controlled trials on this topic.

Acknowledgements

The authors would like to thank William Haskell, Ph.D., Stanford University, for serving as a consultant with specific responsibilities that included reviewing our reference list and providing suggestions for the coding of studies. This study was supported by a grant from the National Institutes of Health-National Heart, Lung and Blood Institute, Award #R01-HL069802 (G.A. Kelley, Principal Investigator).

References

- Anderson, RN.; Smith, BL. National vital statistics reports. 52. National Center for Health Statistics; Hyattsville, MD: 2003. Deaths: leading causes for 2001.
- American Diabetes AssociationDiabetes and cardiovascular (heart) disease2004Available at:http:// www.diabetes.org/diabetes-statistics/heart-disease.jsp(last accessed 8 February 2007)
- 3. National Cholesterol Education Program, National Heart Lung and Blood Institute, National Institutes of Health. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III): final report. Circulation 2002;106:3143–421. [PubMed: 12485966]
- 4. Boudou P, de Kerviler E, Erlich D, Vexiau P, Gautier JF. Exercise training-induced triglyceride lowering negatively correlates with DHEA levels in men with type 2 diabetes. Int J Obes Relat Metab Disord 2001;25:1108–12. [PubMed: 11477494]
- Kaplan RM, Wilson DK, Hartwell SL, Merino KL, Wallace JP. Prospective evaluation of HDL cholesterol changes after diet and physical conditioning programs for patients with type II diabetes mellitus. Diabetes Care 1985;8:343–8. [PubMed: 4042800]
- Ligtenberg PC, Hoekstra JB, Bol E, Zonderland ML, Erkelens DW. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. Clin Sci (Lond) 1997;93:127–35.
 [PubMed: 9301427]
- Raz I, Hauser E, Bursztyn M. Moderate exercise improves glucose metabolism in uncontrolled elderly patients with non-insulin-dependent diabetes mellitus. Isr J Med Sci 1994;30:766–70. [PubMed: 7960690]

8. Ronnemaa T, Marniemi J, Puukka P, Kuusi T. Effects of long-term physical exercise on serum lipids, lipoproteins and lipid metabolizing enzymes in type 2 (non-insulin-dependent) diabetic patients. Diabetes Res 1988;7:79–84. [PubMed: 3396267]

- 9. Tudor-Locke C, Bell RC, Myers AM, Harris SB, Ecclestone NA, Lauzon N, Rodger NW. Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. Int J Obes Relat Metab Disord 2004;28:113–9. [PubMed: 14569279]
- 10. Verity LS, Ismail AH. Effects of exercise on cardiovascular disease risk in women with NIDDM. Diabetes Res Clin Pract 1989;6:27–35. [PubMed: 2649339]
- Petitti, DB., editor. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. Oxford University Press; New York, NY: 2000.
- 12. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. Diabetes Care 2004;27:2518–39. [PubMed: 15451933]
- 13. Baldi JC, Snowling N. Resistance training improves glycaemic control in obese type 2 diabetic men. Int J Sports Med 2003;24:419–23. [PubMed: 12905089]
- 14. Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A, Vuori I. Exercise Training Improves baroreflex sensitivity in Type 2 diabetes. Diabetes 2003;52:1837–42. [PubMed: 12829654]
- 15. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract 2002;56:115–23. [PubMed: 11891019]
- Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. Psychol Methods 2001;6:203– 17. [PubMed: 11570228]
- 17. Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88. [PubMed: 3802833]
- 18. Hunter JE, Schmidt FL. Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge. Int J Sel Assess 2000;8:275–92.
- 19. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
- Hedges, LV.; Olkin, I., editors. Statistical methods for meta-analysis. Academic Press; San Diego, CA: 1985.
- 21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60. [PubMed: 12958120]
- 22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315:629–34. [PubMed: 9310563]
- 23. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–12. [PubMed: 8721797]
- 24. AldersonPGreenSHigginsJPTCochrane Reviewers' Handbook 4.2.1[updated December 2003]
- 25. Kelley GA, Kelley KS, Tran ZV. Retrieval of missing data for meta-analysis: a practical example. Int J Technol Assess Health Care 2004;20:296–9. [PubMed: 15446759]
- 26. Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. Diabetes Care 2003;26:2977–82. [PubMed: 14578226]
- 27. Tsujiuchi T, Kumano H, Yoshiuchi K, Tsujiuchi Y, Kuboki T, Suematsu H, Hirao K. The effect of Qi-gong relaxation exercise on the control of type 2 diabetes mellitus: a randomized controlled trial. Diabetes Care 2002;25:241–2. [PubMed: 11772923]
- 28. Yeater RA, Ullrich IH, Maxwell LP, Goetsch VL. Coronary risk factors in type II diabetes: response to low-intensity aerobic exercise. W V Med J 1990;86:287–90. [PubMed: 2368376]
- 29. Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systemtaic review of controlled trials. Control Clin Trials 1998;19:159–66. [PubMed: 9551280]
- 30. Smith GD, Phillips AN. Inflation in epidemiology: 'The proof and measurement of association between two things; revisited. BMJ 1996;312:1659–61. [PubMed: 8664725]

31. Yoo JS, Lee SJ. A meta-analysis of the effects of exercise programs on glucose and lipid metabolism and cardiac function in patients with type II diabetes mellitus [in Korean]. Taehan Kanho Hakhoe Chi 2005;35:546–54. [PubMed: 16027506]

- 32. Thomas, D.; Elliott, E.; Naughton, G. The Cochrane Library. John Wiley & Sons, UK; Chichester, UK: 2006. Exercise for type 2 diabetes mellitus.
- 33. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001;286:1218–27. [PubMed: 11559268]
- 34. Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J Appl Physiol 2002;3:3–30. [PubMed: 12070181]
- 35. Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K, Wilhelmsen L, Haghfelt T, Thorgeirsson G, Pyorala K, Miettinen T, Christophersen B, Tobert JA, Musliner TA, Cook TJ, Scandinavian Simavastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453–60. [PubMed: 9576425]
- 36. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR Jr. Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. Circulation 1989;79:8–15. [PubMed: 2642759]
- 37. Kraus WE, Houmard JA, Duscha BD, Johnson JL, Ketchum K, Aiken LB, Samsa GP, Houmard JA, Bales CW, Kraus WE. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002;347:1483–92. [PubMed: 12421890]
- 38. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–31. [PubMed: 15381515]
- 39. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998;30:975–91. [PubMed: 9624661]

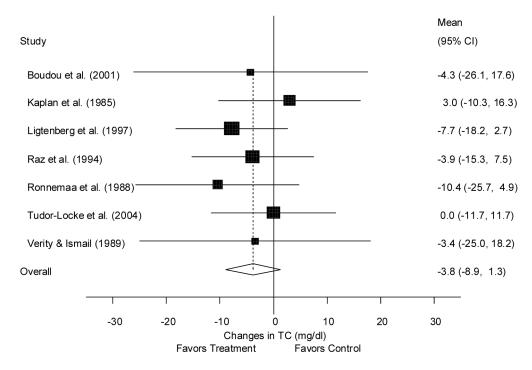


Figure 1. changes in total cholesterol and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond, whereas the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

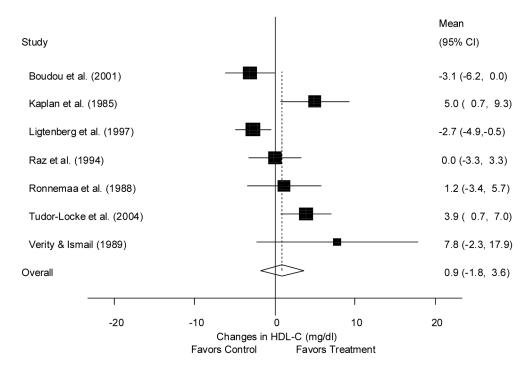


Figure 2. Changes in high-density lipoprotein and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond whereas the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

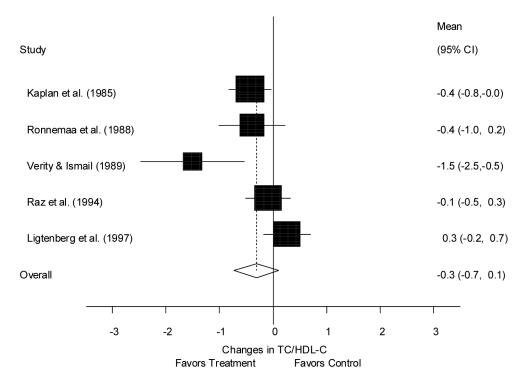


Figure 3. Changes in the ratio of total cholesterol to high-density lipoprotein cholesterol and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond while the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

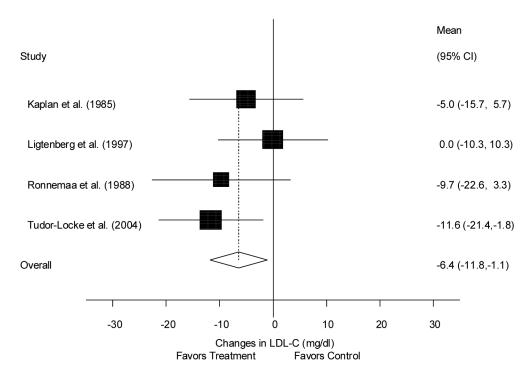


Figure 4. Changes in low-density lipoprotein and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond whereas the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

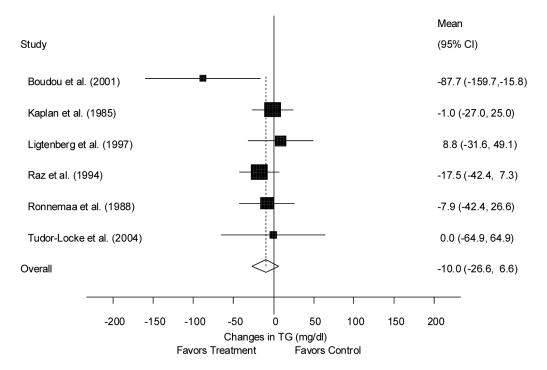


Figure 5. Changes in triglycerides and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond whereas the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

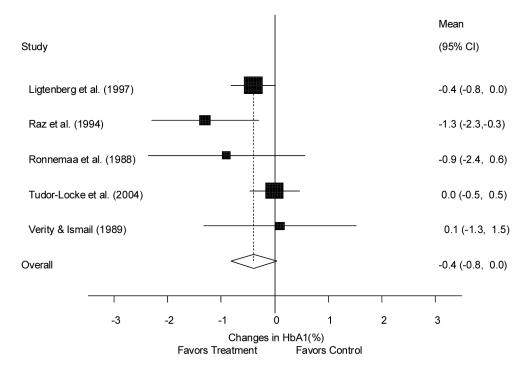


Figure 6.Changes in glycosylated haemoglobin (%) and 95% confidence intervals for each outcome as well as the overall weighted mean difference and 95% confidence interval. The size of the black boxes for each outcome represents the weight given to that outcome. The overall mean difference is shown by the middle of the diamond, whereas the left and right extremes of the diamond represent the corresponding 95% confidence interval. The vertical dashed line represents the overall mean.

Kelley and Kelley

Page 17

Table 1

Characteristics of included studies.

Study	Participants	Exercise intervention	Lipids asessed	Assessment methods
Boudou et al. 2004 ⁴	16 men (mean age = 45 years) assigned to either an exercise $(n = 8)$ or control $(n = 8)$ group	8 weeks of supervised cycle ergometer exercise, 2 days per week, 75% of VO _{2max} , 45 min per session, and intermittent exercise once per week	TC, HDL, TG	Morning after an overnight fast
Kaplan et al. 1985 ⁵	33 sedentary men and women (mean age = 54 years) assigned to an exercise $(n = 18)$ or control (n = 15) group	10 weekly walking sessions over a 10-week period, 40–60 min/session, 60–70% of VO _{2max}	TC, HDL-C, LDL- C, TG, TC/HDL-C	Morning after a 12-hour overnight fast
Ligtenberg et al. 1997 ⁶	51 men and women 55–75 years of age assigned to either an exercise $(n = 25)$ or control $(n = 26)$ group	26 weeks of walking/running, cycling, swimming, rowing, 3 days/week, 50 min/session, 60 –80% of VO _{2max}	TC, HDL-C, LDL- C, TG, TC/HDL-C	Morning after a 12-hour overnight fast and within 72 h of the last exercise session
Raz et al. 1994 ⁷	38 men and women assigned to either an exercise $(n = 19, age = 56.7 \pm 6.2 \text{ years})$ or control $(n = 19, age = 56.5 \pm 6.7 \text{ years})$ group	12 weeks of walking, jogging, swimming, cycling, 3 days/week, 45–50 min/session, 65–70% of MHRR	TC, HDL-C, TG, TC/HDL-C	Morning after a 12-h overnight fast
Ronnemaa et al. 1988 ⁸	25 men and women, 52.5 years of age, assigned to either an exercise $(n = 13)$ or control $(n = 12)$ group	16 weeks of walking, jogging, or skiing, 5–7 days/week, at least 45 min/session, about 70% of VO _{2max}	TC, HDL-C, LDL- C, TG, TC/HDL-C	Morning after an overnight fast
Tudor-Locke et al. 2004 ⁹	47 overweight/obese, sedentary men and women 40–60 years of age assigned to either an exercise (<i>n</i> = 24) or control (<i>n</i> = 23) group	30 min of increased physical activity (> 3000 steps per day) for 16 weeks	TC, HDL-C, LDL- C, TG	Morning after an overnight fast of at least 10 h
Verity and Ismail 1989 ¹⁰	10 sedentary women, 50 -70 years of age, assigned to either an exercise $(n = 5,$ age = 61.20 ± 9.17 years) or control $(n = 5,$ age = 57.20 ± 8.27 years) group	16 weeks of walking, 3 days/ week, 60–90 min/session, 65 –80% of MHRR	TC, HDL-C, TC/ HDL-C	Morning after a 10–12-h overnight fast

Description of studies is limited to those participants and variables that met our inclusion criteria; number of participants is limited to those in which pre- and post-assessment of lipids took place; data reported as mean \pm standard deviation; lipid variables listed are limited to those that met our inclusion criteria, including availability; HDL-C, high-density lipoprotein cholesterol; LDL-C, lowdensity lipoprotein cholesterol; MHRR, maximum heart rate reserve; TC, total cholesterol; TG, triglycerides; TC/HDL-C, ratio of total cholesterol to high-density lipoprotein cholesterol.; VO $_{2max}$, maximum oxygen consumption

NIH-PA Author Manuscript

Baseline characteristics of participants.

NIH-PA Author Manuscript

	Range	45-61	188 - 264 (4.9–6.8)	34-51 (0.9-1.3)	112-162 (2.9-4.2)	4-7	168-219 (1.9 - 2.5)	8-12
Control	$X \pm SD$	54.2 ± 4.9	$220.3 \pm 27.2 \ (5.7 \pm 0.7)$	$43.5 \pm 6.5 (1.1 \pm 0.2)$	$134.3 \pm 22.7 \ (3.5 \pm 0.6)$	5.0 ± 0.8	$188.0 \pm 16.9 (2.1 - 0.2)$	9.7 ± 2.1
	N	7	7	7	4	7	9	4
	Range	45 - 63	202 - 261 (5.2–6.8)	36-56 (0.9-1.4)	120-179 (3.1-4.6)	4-6	164-227 (1.9-2.6)	8-13
Exercise	$X \pm SD$	55.1 ± 5.9	$223.4 \pm 21.6 (5.8 \pm 0.6)$	$44.3 \pm 6.3 (1.1 \pm 0.2)$	$142.1 \pm 26.2 \ (3.7 \pm 0.7)$	5.1 ± 0.7	$193.3 \pm 23.0 \ (2.2 \pm 0.3)$	9.7 ± 2.1
	N	7	7	7	4	7	9	4
	Variable	Age (years)	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	TC/HDL-C	TG (mg/dl)	HbA, (%)

N, number of groups reporting data; X ± SD, mean ± standard deviation; numbers in parentheses represent lipid and lipoprotein outcomes in millimoles (mmol); range represents the means for each group from each study; HbA1, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TC/HDL-C, ratio of total cholesterol to high-density lipoprotein cholesterol; TG, triglycerides. NIH-PA Author Manuscript

Changes in primary and secondary outcomes.

Table 3

Variable	N	X,95% CI	Ò	d	$ m I^2$
Primary outcomes					
TC (mg/dl)	7	-3.8, -8.9 to 1.3 (-0.10, -0.23 to 0.03)	2.7	8.0	0
HDL-C (mg/dl)	7	0.9, -1.8 to 3.6 (0.02, -0.05 to 0.09)	23.2	0.001	74
LDL-C (mg/dl)	4	$-6.4, -11.8 \text{ to } -1.1^{a} (-0.17, -0.31 \text{ to } -0.03)$	2.9	0.4	0
TC/HDL	ß	-0.3, -0.7 to 0.1	12.9	0.01	69
TG (mg/dl)	9	-10.0, -26.6 to 6.6 (-0.11, -0.30 to 0.08)	6.2	0.3	20
Secondary outcome $\mathrm{HbA_{1}}\left(\%\right)^{b}$	ĸ	-0.4, -0.8 to 0	6.5	0.2	39

density lipoprotein cholesterol; P, significance value for Q; Q, heterogeneity value; TC, total cholesterol; TC/HDL-C, ratio of total cholesterol to high-density lipoprotein cholesterol; TG triglycerides N, number of groups reporting data in which a treatment effect could be calculated; X (95% CI), mean, 95% confidence interval; numbers in parentheses represent lipid and lipoprotein outcomes in millimoles (mmol); HbA1, glycosylated haemoglobin; HDL-C, highdensity lipoprotein cholesterol; 12, percentage (%) of inconsistency for study results, calculated from Q statistic; LDL-C, low-

 a Significantly different from zero

b. The number of outcomes for HbA1 differs from the baseline values reported in Table 2 because only four baseline values were reported.